

WHAT IS CLAIMED IS:

1. An infectivity-enhanced conditionally-replicative adenovirus, wherein said adenovirus possesses enhanced infectivity towards a specific cell type due to a modification or replacement of the fiber of a wildtype adenovirus, said modification or replacement results in enhanced infectivity relative to said wildtype adenovirus, and wherein said infectivity-enhanced conditionally-replicative adenovirus has at least one conditionally regulated early gene, said early gene conditionally regulated such that replication of said infectivity-enhanced conditionally-replicative adenovirus is limited to said specific cell type.

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2. The infectivity-enhanced conditionally-replicative adenovirus of claim 1, wherein said cell type is a tumor cell.

3. The infectivity-enhanced conditionally-replicative adenovirus of claim 1, wherein said modification or replacement to the fiber results in coxsackie-adenovirus receptor-independent gene transfer with respect to the type 5 receptor.

4. The infectivity-enhanced conditionally-replicative adenovirus of claim 1, wherein said modification or replacement to the fiber is selected from the group consisting of introducing a ligand into the HI loop of said fiber, replacing said fiber with a substitute protein which presents a targeting ligand, and introducing a fiber knob domain from a different subtype of adenovirus.

5. The infectivity-enhanced conditionally-replicative adenovirus of claim 4, wherein said ligand is selected from the group consisting of physiological ligands, anti-receptor antibodies and cell-specific peptides.

6. The infectivity-enhanced conditionally-replicative adenovirus of claim 4,
wherein said ligand comprises a tripeptide of Arg-Gly-Asp (RGD).

7. The infectivity-enhanced conditionally-replicative adenovirus of claim 4,
5 wherein said ligand comprises a peptide having the sequence CDCRGDCFC.

8. The infectivity-enhanced conditionally-replicative adenovirus of claim 1,
wherein said early gene is conditionally regulated by means selected from the group
consisting of a tissue-specific promoter operably linked to said early gene and a mutation in
10 said early gene.

9. The infectivity-enhanced conditionally-replicative adenovirus of claim 8,
wherein said tissue-specific promoter is from a gene encoding a protein selected from the
group consisting of prostate specific antigen, carcinoembryonic antigen, secretory
15 leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor, CXCR4 and
survivin.

10. The infectivity-enhanced conditionally-replicative adenovirus of claim 1,
wherein said infectivity-enhanced conditionally-replicative adenovirus carries a therapeutic
20 gene in its genome.

11. The infectivity-enhanced conditionally-replicative adenovirus of claim 10,
wherein said therapeutic gene is a herpes simplex virus thymidine kinase gene.

25 12. A method of killing tumor cells in an individual, comprising the steps of:
pretreating said individual with an effective amount of the infectivity-enhanced
conditionally-replicative adenovirus of claim 11; and

administering ganciclovir to said individual.

13. A method of providing adenoviral gene therapy in an individual, comprising the steps of:

5 administering to said individual a therapeutic dose of an infectivity-enhanced conditionally-replicative adenovirus, wherein said adenovirus possesses enhanced infectivity towards a specific cell type due to modification or replacement of the fiber of a wildtype adenovirus, wherein said modification or replacement results in enhanced infectivity relative to said wildtype adenovirus, and wherein said infectivity-enhanced conditionally-replicative adenovirus has at least one conditionally regulated early gene, said early gene conditionally regulated such that replication of said infectivity-enhanced conditionally-replicative adenovirus 10 is limited to said specific cell type.

14. The method of claim 13, wherein said administration is by means selected from 15 the group consisting of intravenously, intraperitoneally, systemically, orally and intratumorally.

15. The method of claim 13, wherein said individual has cancer.

16. The method of claim 13, wherein said cell is a tumor cell.

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17. The method of claim 13, wherein said modification or replacement to the fiber results in coxsackie-adenovirus receptor-independent gene transfer with respect to the type 5 receptor.

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18. The method of claim 13, wherein said modification or replacement to the fiber is selected from the group consisting of introducing a ligand into the HI loop of said fiber,

replacing said fiber with a substitute protein which presents a targeting ligand, and introducing a fiber knob domain from a different subtype of adenovirus.

19. The method of claim 18, wherein said ligand is selected from the group
5 consisting of physiological ligands, anti-receptor antibodies and cell-specific peptides.

20. The method of claim 18, wherein said ligand comprises a tripeptide having the sequence Arg-Gly-Asp (RGD).

10 21. The method of claim 18, wherein said ligand comprises a peptide having the sequence CDCRGDCFC.

22. The method of claim 13, wherein said early gene is conditionally regulated by means selected from the group consisting of a tissue-specific promoter operably linked to said
15 early gene and a mutation in said early gene.

23. The method of claim 22, wherein said tissue-specific promoter is from a gene encoding a protein selected from the group consisting of prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular
20 endothelial growth factor, CXCR4 and survivin.

24. The method of claim 13, wherein said adenovirus carries in its genome a therapeutic gene.